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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	PAPER NUMBER
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/19/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/790,455	HARVEY ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *53-101* is/are pending in the application.

4a) Of the above claim(s) *53-91* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *92-101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/22/04; 3/14/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of claims 92-101 (group III) in the reply filed on October 11, 2006 is acknowledged.

Claims 53-91 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on October 11, 2006.

Claims 92-101 are under consideration.

Drawings

The figures 9-19 of the specification are objected to because sequence listings included in the specification must not be duplicated in the drawing/figures. See C.F.R. 1.58(a) and § 1.83. Applicants are advised that upon issuance of a patent, the complete text of the sequence listing submitted in compliance with 37 C.F.R § 1.821-1.825 will be published as part of the patent. "Applicants should amend the specification to delete any figures which consist only of nucleic acid or protein sequence which have been submitted in their entirety in computer readable format (as SEQ ID Nos) (see

figures 9-19)". In this case, no further detail to the sequence is supplied in the figure and is effectively the SEQ ID number.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 92-101 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by

Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

The office has analyzed the specification in direct accordance to the factors outlines in *In re Wands*. MPEP 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on factors discussed in MPEP 2164.01(a) and the evidence as whole, it is not necessary to discuss each factor in written enablement rejection." These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

The claims are directed to a trisomic avian comprising a cell that contains artificial chromosome comprising heterologous recombination sites that are attP or attB sites. Subsequent claims limit the avian to include a chicken. The claims are further directed to trisomic avian wherein artificial chromosome comprises a heterologous coding sequence encoding a pharmaceutical protein.

The present invention features artificial chromosomes useful as vectors to shuttle transgenes or gene clusters into the avian genome to make modified avians. The specification contemplates delivering the modified chromosome to an isolated recipient cell, the target cell, and progeny that become trisomic (see paragraph 21 of the specification). It is noted that the only use recited for such a modified avian is their use as "bioreactors" for the production of specific proteins (see paragraph 3 and 27). While the specification contemplates that methods of the invention may be used to create any trisomic avian, the guidance provided by the specification do not correlate to a trisomic

avian made by delivering any artificial chromosome of any origin, any size to any avian cell including embryo of any stage or a naturally occurring trisomic chicken resulting in a trisomic avian of any specie. In addition, the specification while providing guidance for using bacterial artificial chromosome for the production of monoclonal antibody in the transgenic chicken in the egg white, the specification does not provide any guidance in terms of any trisomic chicken producing any protein or antibody at any concentration. It is unpredictable if the instantly disclosed trisomic avian, particularly a chicken could produce adequate amounts of exogenous protein that is to be harvested for pharmaceutical or industrial use as contemplated by the specification and claims particularly since claims 97-98 contemplated a trisomic avian comprising a heterologous nucleotide sequence encoding a pharmaceutical substance. Given the lack of guidance provided by the specification it would have required undue experimentation for one of skill in the art to make and use the invention as claimed without a reasonable expectation of success.

As a first issue, instant claims embrace a trisomic avian comprising a cell that contains any artificial chromosome; subsequent claim limits the avian to include a chicken. The specification contemplates "trisomic avian" contain any avian bird that has a 2n+1 chromosomal complement (see paragraph 84 of the published application). In addition, specification teaches that generation of a trisomic avian cell comprising a genetically modified extra chromosome may be an artificial chromosome or an isolated avian chromosome that has been genetically modified. Introduction of the extra chromosome to an avian cell will generate a trisomic cell with 2n+1 chromosomes (see

paragraph 130 of the specification). It is noted that as recited claims 92-101 embrace trisomic avian comprising any cell comprising any artificial chromosome comprising a heterologous nucleotide encoding any pharmaceutical substance without limiting to any base length. Given the broadest reasonable interpretation instant claims require a trisomic avian comprising a cell comprising an artificial chromosome comprising any pharmaceutical substance including all the three human antibody loci that includes heavy chain, kappa light chain and lambda light chain or any protein of any size, by any means. It is noted that prior art teaches trisomy occurred naturally in chicken and an extra copy of one or more of the chicken chromosomes were compatible with normal development and reproductive capacity (Miller et al Proc. Natl. Acad. Sci. U.S.A. 93: 3958-3962 (1996), IDS; Muscarella et al., J. Cell Biol. 101: 1749-1756, 1985, IDS see abstract). However, prior art at the time of the invention also teaches a high degree of unpredictability in maintaining very large mega base length exogenous DNA fragments in any nonhuman animal. A general review of the art teaches that yeast artificial chromosomes (YACs), SATAC and human artificial chromosomes (HACs) are the primary vectors that maintain such large DNA fragments in nonhuman species such as mice. The prior art is generally silent on teaching delivering artificial avian chromosome to any avian including chicken or delivering HAC or SATAC comprising nucleotide-encoding protein of any size length to any cell including somatic cell of naturally occurring trisomic chicken to produce pharmaceutical substance. Kuriowa et al (Nature Biotechnology, 18:1086-1090, 2000) teaches the unpredictability of using fragments of human chromosomes as vectors. Kuriowa et al state, "Human chromosomes (hChrs) or

their fragments have been used to introduce large segments of human genomic DNA into mice. However, it has been reported that the mitotic stability of hChrs in mice varies among human chromosomes and it is difficult to stably maintain any type of human chromosome in order to perform functional analyses in mice. Furthermore, it is difficult to introduce defined regions of human chromosomes into mice because the fragmentation of human chromosomes can occur randomly (page 1086, col. 1, paragraph 2)". It is noted that instant specification teaches cytoplasmic injection of bacterial artificial chromosomes (See example 10 of the specification) comprising light and heavy chain human antibody loci that are genetically transmissible. It is noted that prior to instant invention while reviewing strategies to engineer human chromosome, Saffery et al (J Gene Med. 2002 Jan-Feb;4(1):5-13) describe problems associated with the production of useful human engineered chromosome (HEC) including size and difficult to fully characterize, especially those containing highly repetitive DNA (see page 11, column 2, lines 4-15). It is noted that Saffery et al state that "the large size of HECs also makes them difficult to manipulate in terms of the introduction of genes and the transfer from cell to cell in an intact form. Present methodologies do not readily lend themselves to delivering chromosomes of this size to *in vivo* cell targets" (see page 12, column 1, paragraph 1). Saffery et al describe that the specific production of a human satellite artificial chromosome (SATAC) that shows a 95% retention rate after 50 generations, demonstrating mitotic stability and persistence of β-galactosidase expression over several generations. However, Saffery et al states "SATACs produced by these procedures are typically tens to hundreds of megabases in size, contain

substantial amounts of different classes of repetitive satellite DNA, and are highly complex in structure. Saffery et al emphasize that structural mapping and full sequence characterization of these chromosomes are likely to be impossible (see page 8, column 1, and paragraph 2). Thus, the lack of control over their mode of formation produces the same drawbacks as HECs derived using *de novo* approaches, which does not permit control over gene copy number or the structural integrity of the genes incorporated into the HECs (see page 8, paragraph 1, lines 101-20). In addition, Irvine et al (Trends Biotechnol. 2005; 23(12): 575-83) report that "there are several different methods for the transfer of HECs between cell types but, with the exception of microcell-mediated cell transfer (MMCT), methods for transferring HECs into human somatic cells require an initial purification step to isolate HECs away from other human chromosomes and chromosome fragments" (see page 579, column 1, paragraph 2). It is apparent from the cited art that structural mapping, sequence characterization of SATAC was evolving and not resolved at the time of filing of this application. It is further noted that breadth of instant claims 92-101also embraces a trisomic avian comprising a cell that contains an artificial chromosome comprising a heterologous nucleotide sequence encoding base length of any size. Prior to instant invention, Giraldo et al (Transgenic Res. 2001; 10(2): 83-103) while reviewing transgenic animals carrying either BAC or PAC transgene describe that such transgenic animals have been generated with comparable efficiencies with animals carrying a limited number of integrated transgene copies (<5). It is noted Giraldo et al state "Unfortunately, not all BAC/PAC transgenes integrate in the host genome as intact DNA molecules. Similar to YACs, rearrangements and

insertion of fragmented transgenes can occur with BACs suggesting that rearrangement appears to be primarily related to trans gene size, irrespective of YAC or BAC origin". Giraldo et al also disclose that "relatively small genes (<100 kb) can be analyzed with BACs/PACs, whereas bigger loci require the use of YACs (<1.0Mb) (see page 94 col. 2, para. 3 bridging to page 95, col. 1). Thus, cited art clearly teaches incorporating nucleotide sequence encoding pharmaceutical substance of any size in any artificial chromosome of any size for producing pharmaceutical substance is unpredictable. The specification provides no specific guidance or working examples commensurate with the breadth of the claims to allow an artisan to overcome such art-recognized unpredictability of using any artificial chromosome of any size to deliver mega size nucleic acid such as one exemplified in the instant application. Therefore, given the lack of guidance provided by the specification it would have required undue experimentation for one of skill in art to make and use the invention as claimed without a reasonable expectation of success.

As a second issue, independent claims 92-101 embrace a trisomic avian comprising a cell containing an artificial chromosome. The specification contemplated stage X blastodermal cells can be fused with isolated microcells and then transplanted back into to stage X embryos or fused to somatic cells to be used as nuclear donors for nuclear transfer (see paragraph 134 of the published application). Given the broadest reasonable interpretation, as recited instant claims also embrace introducing a chromosomal vector comprising a transgene in any cell including somatic cell and using methods such as transferring the nucleus of the cell into any enucleated recipient cell

and transferring recipient cell into a recipient avian that produces an offspring. The state of art summarized by the references of Wolf et al (Journal of Biotechnology 65: 99-110, 1998); Stice et al (Therigeneology, 1998, 49: 129-138); Yanagimach et al (Molecular and Cellular Endocrinology, 2002, 187, 241-248); Oback and Wells (Cloning and Stem Cells, 2002, 4, 169-174) disclose limitation of routine method of nuclear transfer. For instance, Wolf et al emphasize several factors that influence embryo cloning by NT, such as the state of development and cell cycle of the donor cells, the choice of recipient cell, the method of activation of oocyte (see entire article). The specification does not provide any guidance to these parameters. Stice et al reported timing of embryonic genome activation might be partly responsible for species-specific differences. Stice et al further noted that method used for cloning sheep where the donor cell was in G0 could not be used in other animal species (see the last paragraph on page 131). This clearly suggests that method used in one animal or species could not be used in another animal or species, the specification does not provide any guidance how claimed method would be practiced in any avian cell. Yanagimachi et al state that "perhaps no single protocol for cloning that works for all species, because, the characteristics of an oocyte and donor cells are from species to species. A protocol that is best for a given species may not be suitable for another species. Technical details must be worked out for each species". It is emphasized that applicants have provided no guidance in this regard. In summary, the specification as filed is not enabling for the claimed invention because a trisomic avian comprising a cell containing artificial chromosome by process of nuclear transfer was not predictable. It is further noted that

specification also contemplates transfection of blastodermal cells isolated from stage X embryos with isolated mitotic chromosomes (see para. 133 of the published application). The state of the art is such that blastodermal technology to produce transgenic avian was unpredictable and evolving at the time of filing of this application. Ivarie (Trends in Biotechnology, 2003, 14-19) cites Pain who describes long term culture of non-transfected, blastodermal cell that provided germline transmission, however, no transgenic birds have been made using transfected ES cell or PGCs. The biggest obstacle to overcome in making transgenic birds using transfected ES cell or PGCs is the loss of germline competence during culture of transfected ES cells and PGCs (see page 14, column 2, paragraph 3 and page 17, column 1, paragraph 2 and last two sentences bridging to columns 1-2 page 17 column 2, last sentence). Therefore, at the time of filing of this application, transgenic avians could not be accomplished using ES or blastodermal cells. The specification fails to provide sufficient guidance to make any trisomic avians and therefore, an artisan would have required extensive experimentation to practice the claimed invention by using nuclear transfer or blastodermal cells and such experimentation would have been undue since the experimentation was not routine, and the state of the art was unpredictable and the specification did not teach how to address the limitation and unpredictable nature of the invention.

As a third issue, the guidance provided by the specification correlated only to cytoplasmic injection of the BAC containing a 70-kbp segment of the chicken ovomucoid gene with the light and heavy chain cDNAs for a human monoclonal antibody in stage I

embryos at a single site of the chicken (see example 9 ad 10). It is emphasized that specification does not provide any evidence that exemplified transgenic chicken is a trisomic chicken. Furthermore, it is unpredictable if a chimeric chicken could produce adequate amounts of exogenous protein that is to be harvested for pharmaceutical use using any artificial chromosome as vector comprising any promoter injected via any route as recited in claims 92-99 and 101. In addition, claims 92-101 embrace avians subsequently limiting to chicken that do not require any specific age or time of administering the vector to the avians. The specification while provides prophetic guidance for mammalian artificial chromosome and exemplified BAC that is administered to stage I embryos that are transferred to the oviduct of recipient avian (see example 10) resulting in chimeric avians. The specification does not provide any specific guidance on whether germline transmission is maintained in subsequent progeny. Although, prior art teaches that an extra avian chromosome 16 could be maintained in a naturally occurring chicken with normal reproductive cycle, neither specification nor prior art provide any guidance whether delivering an artificial avian chromosome would result in trisomic chicken with a stable genome. Brown et al (Curr Opin Genet Dev. 1996 Jun 1; 6(3): 281-8, and Brown et al Trends in Biotechnology, 18, 218-223) while reviewing the frequency of recombination in mammalian somatic cell, (see page 282, column 2, paragraph 3 to page 283) describes "whether these chromosome vectors could be transmitted to next generation through the germline transmission, a crucial issue for potential utility of this procedure remains unpredictable for most of the species". It is art recognized that possibility of an extra chromosome

might inhibit the differentiation of ES cell into functional germ cell leading to sterility of sterility in some chimaeras. These observations are supported by Brown, who addresses the requirement for mini-chromosomes to pass through meiosis. Brown states that male meioses are more sensitive to the presence of unpaired chromosomes than female meioses and an unpaired marker chromosome will often block male meiosis during the first division. Brown further describes that the presence of the mini-chromosome in the germline of a male, might render that animal infertile. Brown et al emphasize that the size and sequence requirements for pairing and exchange in mice, however, have not been established and therefore it is unclear whether this approach will work (see page 287, column 1, paragraph 1). Thus, it is apparent in spite of prior art being silent of using MAC or avian artificial chromosome for making trisomic avians comprising a cell that contains any artificial chromosome; the prior art for using artificial chromosome, as vector was not completely resolved in many other species. It is also noted that while the claims are directed to trisomic avian comprising a heterologous nucleotide including a coding sequence for a pharmaceutical substance (see claim 97-98). The specification teaches that such a therapeutic substance would be produced in the chicken eggs, the specification failed to quantify the amount of pharmaceutical substance actually produced in the trisomic avians' eggs. The specification contemplates to express, in large yields and at low cost, a wide range of desired proteins including those used as human and animal pharmaceuticals, in the transgenic avians (see paragraph 27 of the published application), but such appeared to be a prophetic teaching as the trisomic avians were not made with higher yield or any

specific yield of proteins. It would be unpredictable if trisomic avian embraced by the claims could produce any pharmaceutical substance if they produced exogenous protein in small quantities. Ivarie et al (Trends in Biotechnology, 2003 21(1): 14-19), observed that exogenous protein produced by transgenic chickens in the range of 38μg/ml was far below those required for commercialization (see the section bridging pages 15-16). As such, the specification does not appear to provide guidance correlating the exemplified chicken (see example 9-10) to produce protein or antibody or any other protein, in enough quantity particularly in light of the observations of Ivarie. Finally, the specification has not provided guidance with respect to levels of exogenous protein expression or duration of expression of exogenous protein. Moreover, it is apparent from the lack of guidance provided by the specification, would require further experimentation to practice the instantly claimed trisomic avian such that a relevant amount of exogenous pharmaceutical substances are produced as embraced by claims 97-98. Therefore, it is unpredictable if the trisomic avian would result production of any desired pharmaceutical substance in sufficient amount. An artisan would have to perform undue experimentation to make and use the invention as recited in instant application.

As a third issue, the claims 92, 94-101 broadly embraces creation of any trisomic avian subsequently limiting to chicken, quail and turkey. The specification contemplated that avians including chicken, turkey, duck, goose, quail, pheasants, parrots, finches, hawks, crows and ratites including ostrich, emu and cassowary, as well as strains of turkeys, pheasants, quails, duck, ostriches and other poultry commonly bred in

commercial quantities are embraced by the invention. It is noted that the term "avian" also may denote "pertaining to a bird (see published specification, paragraph 55). The specification has provided guidance correlating to creation of chimeric chicken by cytoplasmic injection of a nucleic acid molecule encoding pharmaceutical substance of interest directly into stage I embryo. As discussed above, the trisomic avian could not produce relevant amounts of therapeutic for collection. The guidance provided by the specification does not extrapolate to all other avians embraced by the claims. Particularly, an extrapolation cannot be made to other avians in light of the biological diversity embraced by the claims. There is no evidence of record correlating the biological processes of egg production between species that would enable one of skill in the art to extrapolate the working example of chicken to all the other species of birds embraced by the claims to produce enough quantity of protein. In addition, to the general lack of guidance with respect to use of other species embraced by the claims, the other species embraced by the claims are subject to all of the issues discussed above. Given the lack of guidance provided by the specification it would have required undue experimentation for one of skill in art to make and use the invention as claimed without a reasonable expectation of success.

As a final issue, the specification does not disclose whether any artificial chromosome other then BAC would be maintained stably in the any trisomic avian. While the art teaches that artificial chromosomes are stable, the introduction of an artificial chromosome containing a heterologous nucleotide sequence encoding any protein in producing trisomic avian will be unpredictable as stated earlier in this office

action (supra). Furthermore, it would be unpredictable whether artificial chromosome of different origin would function in different species of birds as contemplated by instant invention, given the unpredictability in maintaining chromosome in the germline (Brown et al, supra). An artisan would have to carry out extensive experimentation to make use of the invention, and such experimentation would have been undue because of unpredictabilities in getting germline transmission in chimeric trisomic avian comprising a cell containing any artificial chromosome.

In conclusion, in view of breadth of the claims and absence of a strong showing by applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by applicant is not enabled for the claimed inventions. The specification and prior art do not teach method of trisomic avian for producing a therapeutic substance. An artisan of skill would have to perform undue experimentation to practice the invention as claimed because the art of trisomic avian comprising a cell containing any artificial chromosome for producing exogenous therapeutic protein was unpredictable at the time of filing of this application as supported by the observations in the art record.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 98 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 98 is vague and indefinite because of recitation of term "pharmaceutical substance". It is not apparent from the specification what is included or excluded by this nucleotide sequence that includes a coding sequence for a pharmaceutical substance. Since it is subject to different interpretation depending on the Artisan, the meets and bound of the claimed invention cannot be determined. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 92, 94, 97-98 and 99 are rejected under 35 U.S.C. 102(e) as being anticipated by Hadlaczky et al (US patent application no 2004/0143861, effective filing date 04/10/1996).

It is noted that the instant specification defines the term "avian" to denote "pertaining to a bird such as "an avian (bird) cell (see published specification, paragraph 55).

Prior to instant invention, Hadlaczky et al taught a transgenic nonhuman animal including bird obtained by introducing an embryo comprising a satellite artificial chromosome into a bird; and allowing the embryo to develop into a transgenic bird comprising a satellite artificial chromosome comprising heterologous DNA that encodes a therapeutic product (claims 1, 14-16, pages 42-43). It is emphasized that Hadlaczky et al also disclosed that the host could be any species including bird-comprising MACs containing heterologous nucleotide sequence, which could be introduced and effected or if required to identify species-specific centromeres and/or functional chromosomal units and then using the resulting centromeres or chromosomal units as artificial chromosomes (see paragraph 133, 134). Thus, the teaching of Hadlaczky et al also embrace delivering avian artificial chromosome to make transgenic bird meeting the claim limitation of trisomic chicken. In addition, Hadlaczky et al contemplated operative linkage of heterologous DNA to regulatory and effector sequences of nucleotides, such as promoters (see paragraph 53). It is emphasized that the method disclosed by Hadlaczky et al uses the gene of interest into the lambda neo-chromosome by virtue of homologous recombination with the heterologous DNA in the chromosome (see example 7 and paragraphs 85 and 221). Thus, the transgenic bird disclosed by Hadlaczky et al and those embraced by the instant claims appear to be structurally same. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When

the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433.

Accordingly, Hadlaczky et al anticipate claims 92, 94-95 97-98 and 99.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 92-101 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of copending Application No. 11/068155.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to transgenic avians that uses serine recombinase mediated recombination at the heterologous recombination site. Since the specification of the '155 contemplated pHiC31 integrase mediated recombination between att site with in the nucleic acid molecule and an attachment site within the genomic DNA of avian cell and dependent embrace same production of heterologous coding sequence comprising pharmaceutical protein. Furthermore, instant application also discloses use of artificial chromosome to produce a trisomic avian comprising a cell that contains an artificial chromosome comprising nucleotide encoding a pharmaceutical protein using the method essentially recited in application '155. Claim 92-101 of application '455 application are directed to a trisomic avian. Subsequent claims are directed to a trisomic avian comprising a cell that contains an artificial chromosome subsequently limiting to a chicken comprising serine recombinase that mediates the recombination at the heterologous recombination site. The claims are further directed to trisomic avian comprising an artificial chromosome that comprises a heterologous nucleotide sequence. Subsequent claims limit the avian to include artificial chromosome comprising a heterologous recombination site is attP or coding sequence, whereas claims in '155 are directed to a transchromosomic avian obtained by introducing into an avian cell an artificial chromosome comprising a centromere.

Subsequent claims limit the centromere to include an insect or mammalian or avian centromere. Thus, the claims of application no 11/068155 differs only with respect to scope of avian artificial chromosome that could be used in the method for producing trisomic avians for producing desired polypeptide, as claimed in instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 92-101 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16, 22 of copending Application No. 11/362,064.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to methods of producing transgenic avians that uses serine recombinase mediated recombination at the heterologous recombination site. The specification of the '064 contemplated a transgenic avian which is same as one disclosed in instant application comprising a heterologous recombination site with in the nucleic acid molecule and an attachment site within the genomic DNA of avian cell. Furthermore, instant application also discloses use of artificial chromosome to produce pharmaceutical protein using the method essentially recited in application '064. Claims 92-101 of application '455 application are directed to a trisomic avian. Subsequent claims are directed to a trisomic avian comprising a cell that contains an artificial chromosome subsequently limiting to a chicken comprising serine recombinase that mediates the recombination at the

heterologous recombination site. The claims are further directed to trisomic avian comprising an artificial chromosome that comprises a heterologous nucleotide sequence, whereas claims 1-16 and 23 of application '064 application are directed to an avian obtained by introducing the artificial chromosome into an avian embryo; maintaining the embryo under conditions suitable for the embryo to develop and hatch as a chick; and maintaining the chick under conditions suitable to obtain a mature avian wherein the artificial chromosome is present in the genome of the mature avian. It is noted that claims 1-16 and 23 are directed to a transgenic avian comprising a cell that contains an artificial chromosome subsequently limiting to a chicken comprising heterologous recombination site. Thus, the claims of application no. '064 differs only with respect to broader scope of avian artificial chromosome and recombination site that could be used in the method for producing avians for producing desired polypeptide, as claimed in instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 92-101 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 and 25-28 of copending Application No. 11/193,750.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to a transgenic avians that uses serine recombinase mediated recombination at the heterologous recombination site to

produce polypeptide or antibodies. Since the specification of the '750 contemplated serine recombinase mediated recombination between att site with in the nucleic acid molecule and an attachment site within the genomic DNA of avian cell and dependent embrace production of protein. The claim 92-101 of application '455 application are directed to a trisomic avian. Subsequent claims are directed to a trisomic avian comprising a cell that contains an artificial chromosome subsequently limiting to a chicken comprising serine recombinase that mediates the recombination at the heterologous recombination site. The claims are further directed to trisomic avian comprising an artificial chromosome that comprises a heterologous nucleotide sequence, whereas claim 1-13 and 25-28 of application '750 are directed to a transchromosomic avian comprising a transgene comprising greater than about 5,000 nucleotides. It is noted that subsequent claims limit the avian to include a chicken, quail or turkey. It is also noted that specification contemplate using serine recombinase that mediates the recombination at the heterologous recombination site. Thus, the claims of application no 11/193,750 differ only with respect to scope of artificial chromosome that also includes an avian artificial chromosome that could be used for producing transgenic avians for producing desired polypeptide as claimed in instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Hadlaczky et al (US 6,743,967)
Lindenbaum et al (WO 02/097059, dated 12/5/2002).
Calos (US 6,632672, dated 10/14/2003, IDS)
Kuhn et al (WO 02/38613, dated 5/16/2002; IDS)
Muscarella et al, J. Cell Biol. 101: 1749-1756, 1985, IDS
Macarthur et al (WO 97/47739, IDS)
Tanaka et al (J Repord. Fert., 1994, Vol. 100, 447-449, IDS)

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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